

PTO: 2003-5084

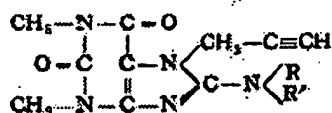
Japanese Published Examined Patent Application (Kokoku Koho) No. S37-4895, Patented Date: June 16, 1962; Application No. not listed; Application Date: August 18, 1959; Inventor: Michio Nakanishi; Applicant: Yoshitomi Pharmaceutical Corporation; Japanese Title: 7,8-Chikan Teofirin Yuudoutai no Seizou Houhou (Method for Production of 7,8-Substituted Theophylline Derivatives)

## Method for Production of 7,8-Substituted Theophylline Derivatives

### Detailed Description of the Invention

This invention pertains to a producing method for 7,8-substituted theophylline derivatives.

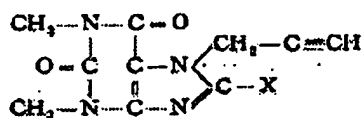
The invention is a method for production of 7,8-substituted theophylline derivatives as indicated by the following general formula:



(In the formula, R and R' represent hydrogen, an aliphatic group, aromatic group, araliphatic group or both aliphatic and aromatic groups with a different top ring formed by closing the ring with nitrogen), characterized in that



(In the drawing, R and R' indicate the same components as disclosed above) is reacted to 8-halogeno-7propyne (2')-theophylline as indicated by the following formula:



(In the formula, X represents halogen).

All of the 7,8-substituted theophylline derivatives obtained by the method of the invention are new substances as not listed in any references. In the medical field, the

derivatives are valuable compounds as cardiotoxic diuretics or the synthetic intermediate substances. These substances can form inorganic acid and organic acid salts. For example, the following types of the salts are formed: hydrochloride; sulfate; nitrate; succinate; citrate; tartrate; picolate; sulfonate; a quaternary ammonium salt.

Any type from chlor, bromine or iodine is used as the 8<sup>th</sup> halogenide of 8-halogeno-7 propyne (2') theophylline that is used as a raw substance for the method of the invention. This substance is produced by a reaction between propargyl halogenide and 8-halogeno theophylline.

According to the method of the invention, 8-halogeno-7 propyne (2') theophylline is aminated by reacting ammonium or primary amine and secondary amine to it. As for these amines, the following types of primary and secondary amines wherein R and R' of

the aforementioned general formula  $\text{HN} \begin{matrix} \nearrow \text{R} \\ \searrow \text{R}' \end{matrix}$  represent an aliphatic, aromatic group, aroma-aliphatic group or both aliphatic and aromatic groups with a different top ring formed by closing the ring with nitrogen are selected as needed as long as the reaction does not develop any problems: methyl amine; diethyl amine; aniline; pentyl amine; phenylethyl amine; morpholine; pyrrolidine; piperidine. These amines can further contain an oxy group, a carboxy group, an alkoxy group, a carboalkoxy group or an alkyl group formed by these groups substituted.

The method of the invention is carried out under the presence or absence of a deoxidizer by using a conventional method. At this time, a sealing or pressurizing means can be applied depending on the types of amines. Or the method can be used at a normal temperature, a high temperature or at a reflux by heating.

In this reaction, if ammonia and amines as crude substances are excessively used, they act as deoxidizers. Because of this effect, no regular deoxidizers are required. When the base property of amines is low, conventionally used deoxidizers, for example, dehalogenized hydrogen agents that do not involve in the reaction can be added, such as potassium carbonate, sodium bicarbonate, caustic potassium, pyridine and triethyl amine. If the reaction does not smoothly progress, copper sulfate, copper chloride and a copper powder are used as catalysts.

As for reaction solvents, any solvents can be selected as long as the reaction does not develop any problems. Solvents that dissolve the crude substances are usually used: alcohol; benzole; chloroform.

#### Embodiment 1

The following substances at the following amounts are circulated in alcohol at 150 c.c. for 7 hours by a heating means: morpholine at 4.5g; 8-bromine-7 propyne (2') theophylline at 17g; potassium carbonate at 4.5g. After the heating, the solution is filtered. When the alcohol in the filtered solution is distilled and when the remaining portion is purified from alcohol, 8-morpholino-7 propyne (2') theophylline at a 174°C melting point is obtained.

#### Embodiment 2

Piperidine at 4.2g is used in lieu of morpholine as in Embodiment 1. When a reaction process is applied as similar to as in Embodiment 1, 8-piperidino-7 propyne (2') theophylline at a 183°C melting point is obtained.

### Embodiment 3

Diethyl amine at 3g and 8-bromine-7-propyne-(2')-theophylline at 4.5g are supplied in a pressure resistant bottle with alcohol at 80 c.c. The solution is then heated in the water bath for 8 hours. After this, alcohol is distilled. When the deposited crystal is purified from water containing methanol, 8-diethyl amino-7-propyne-(2')-theophylline at a 92°C melting point is obtained.

### Embodiment 4

The following substances at the following amounts are circulated in alcohol at 150 c.c. for 7 hours: N-methyl piperadine at 1.77g; 8-buromine-7-propyne-(2')-theophylline at 5g; potassium carbonate at 1.16g. After the solution has been filtered, alcohol is distilled. When the remaining portion is purified from water, 8-(N-methyl-N'-piperadino)-7-propyne-(2')-theophylline at a 146°C melting point is obtained.

### Embodiment 5

The following substances at the following amounts are heated in alcohol at 300 c.c. for 10 hours: 8-bromine-7-propyne (2')-theophylline at 14g; 2-phenyl isopropyl amine at 6.4g; potassium carbonate at 3.4g. After this, alcohol is distilled. When the remaining portion is purified from methanol, 8-(2-phenyl isopropyl amino)-7-propyne theophylline at a 234 to 235°C melting point is obtained.

### Embodiment 6

The following substances at the following amounts are heated in alcohol at 150 c.c. for 10 hours: 8-bromine-7-propyne theophylline at 7g; 3-(2-ethyl hexoxy)-propyl amine at 4.4g; potassium carbonate at 1.7g. After this, when a process as similar to as in Embodiment 5 is applied, 8-[3-(ethyl hexoxy)-propyl amino]-7-propyne theophylline at a 136 to 137°C melting point is obtained.

#### Embodiment 7

The following substances at the following amounts are heated in alcohol at 150 c.c. for 10 hours: 8-bromine-7-propyne theophylline at 7g; 3-diethyl amino propyl amine at 3.1g; potassium carbonate at 1.7g. After this, when a process as similar to as in Embodiment 5 is applied, 8-(3-diethyl amino propyl amino)-7-propyne theophylline at a 184 to 185°C melting point is obtained.

#### Embodiment 8

The following substances at the following amounts are mixed in alcohol: 8-bromine-7-propyne-(2')-theophylline at 7g;  $\gamma$ -[ $\beta$ -( $\beta$ -oxyethoxy)-ethoxy]-propyl amine at 4.6g; potassium carbonate at 2.15g. When a reaction process is applied as similar to as in Embodiment 5, 8- $\gamma$ -[ $\beta$ -( $\beta$ -oxyethoxy)-ethoxy]-propyl amino-7-propyne-(2')-theophylline at a 151°C melting point is obtained.

#### Embodiment 9

The following substances at the following amounts are mixed in alcohol: 8-bromine-7-propyne-(2')-theophylline at 7g;  $\gamma$ -morpholino propyl amine at 4.5g; potassium